

The Absolute Configuration of Menthyl Methylphosphinate: A Reassignment and Its Stereochemical Consequences

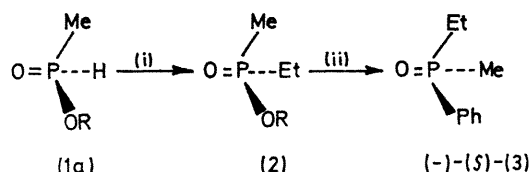
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Summary The absolute configurations of the epimeric menthyl methylphosphinates (**1**) are the reverse of those previously reported, and the stereochemistry of reactions which depend on (**1**) for a configurational anchor is reassessed in the light of this finding.

THE absolute configuration of menthyl methylphosphinate (**1**) is open to question,¹ and we now present chemical evidence that an earlier tentative assignment² is in error.

Our absolute configurational assignment rests on the chemical correlation of (**1a**) and (–)-(*S*)-ethylmethylphenylphosphine oxide (**3**) (Scheme 1). Reaction of phenylmagnesium bromide with menthyl ethylmethylphosphinate (**2**), obtained by alkylation of a 70:30 mixture of (**1a**) and (**1b**) with ethyl iodide and sodium hydride in dimethylformamide, provided (–)-(*S*)-(**3**),³ $[\alpha]_D - 3.0^\circ$ (MeOH). Similar treatment of a 15:85 mixture of (**1a**) and (**1b**) gave (+)-(*R*)-(**3**), $[\alpha]_D + 6.1^\circ$ (MeOH). Since alkylation of menthyl phenylphosphinate under comparable conditions proceeds with predominant retention of configuration at phosphorus,⁴ and since reactions of Grignard reagents with phosphinates occur with predominant inversion of configuration at phosphorus,³ the chirality at phosphorus in (**1a**) is assigned as *R* and that in (**1b**) as *S*, *i.e.*, the reverse of the previous assignment.^{2†} Consequently, the stereochemistry of reactions which feature (**1**) as a configurational anchor^{5,6} requires reassessment.



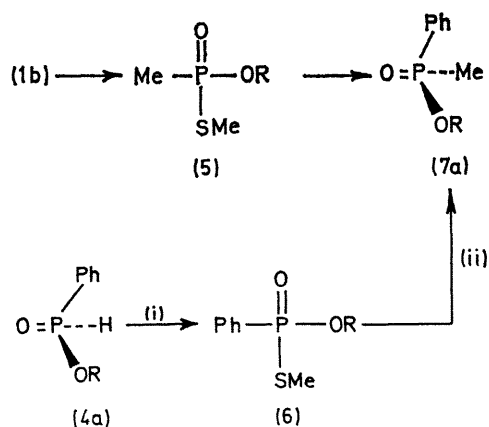
SCHEME 1. R = (–)-menthyl. Reagents: (i) ethyl iodide and sodium hydride in dimethylformamide at *ca.* 40°; (ii) phenylmagnesium bromide in benzene for 20 h under reflux.

Since free-radical addition of (**1b**) to alkenes produces menthyl (*R*)_P-alkylmethylphosphinates,⁶ this reaction is now recognized to proceed with retention of configuration, and not with inversion, as previously claimed;⁶ it thus parallels the corresponding reaction of menthyl phenylphosphinate (**4**).¹

Since thiomethylation of (**1b**) under various conditions (reaction with sulphur and methyl iodide, with *NN*-diethylmethanesulphenamide, or photochemically with dimethyl disulphide)^{5,6} followed by reaction of the resultant menthyl *S*-methyl methylphosphonothioate (**5**) with phenylmagnesium bromide gives menthyl (*R*)_P-methylphenylphosphinate⁶ (**7a**) (Scheme 2), the two-step reaction sequence is now

recognized to proceed with *overall* retention of configuration, and not with inversion, as previously suggested.⁶ We have found that the analogous conversion of (**4**)⁴ into (**7**) *via* menthyl *S*-methyl phenylphosphonothioate (**6**) also occurs with overall retention of configuration.

Thiomethylation of (**4**) was carried out by reaction of a 85:15 mixture of (**4a**) and (**4b**) with an equimolar amount of dicyclohexylamine and 1 equiv. of sulphur in diethyl ether, followed by alkylation of the resulting adduct with methyl iodide in benzene. This procedure provided a *ca.* 85:15 mixture of (**6a**) and (**6b**)[‡] in 85% yield. Similar treatment of a 40:60 mixture of (**4a**) and (**4b**) afforded a 40:60 mixture of (**6a**) and (**6b**). The photochemical thiomethylation of (**4**) was complicated by photoepimerization of (**6**). Irradiation (Rayonet Photochemical Reactor equipped with 253.7 nm lamps) of a 85:15 mixture of (**4a**) and (**4b**) and a five-fold molar excess of dimethyl disulphide in *n*-heptane for 0.5 h afforded a 60:40 mixture of (**6a**) and (**6b**). Irradiation of a 15:85 mixture of (**4a**) and (**4b**) under similar conditions provided a 40:60 mixture of (**6a**) and (**6b**). Further irradiation led to a nearly equimolar mixture of (**6a**) and (**6b**).§ Reaction of a 35:65 mixture of (**6a**) and (**6b**) with methylmagnesium bromide afforded in 70% yield a 35:65 mixture of (**7a**) and (**7b**). Similar treatment of diastereomerically homogeneous (**6a**) gave (**7a**). Since the absolute configurations of the epimers of (**4**) and (**7**) have been established^{4,3} as (*R*)_P for (**4a**) and (**7a**), and as (*S*)_P for (**4b**) and (**7b**), it follows that overall retention of configuration at phosphorus obtains for the conversion of (**4**) into (**7**) *via* (**6**).



SCHEME 2. R = (–)-menthyl. Reagents: (i) sulphur and dicyclohexylamine in diethyl ether for 4 h under reflux, followed by methyl iodide in benzene for 8 h at 50°; or dimethyl disulphide in *n*-heptane with u.v. irradiation; (ii) methylmagnesium bromide in tetrahydrofuran for 0.5 h under reflux.

† Thus the epimer of (**1**) with m.p. 42° and $[\alpha]_D - 96.6^\circ$ (C₆H₆) is now identified as (**1b**), *i.e.*, as (*S*)_P.

‡ Satisfactory elemental analyses were obtained. The ¹H n.m.r. spectrum (CDCl₃) of (**6a**), m.p. 76–76.5°, $[\alpha]_D - 141^\circ$ (C₆H₆), featured: SCH₃, d, τ 7.84, ³J_{PH} 13.5 Hz. The ¹H n.m.r. spectrum of (**6b**), m.p. 46.5–47.5°, $[\alpha]_D + 25^\circ$ (C₆H₆), featured: SCH₃, d, τ 7.86, ³J_{PH} 13.6 Hz. Diastereomeric compositions were determined by integration of the thiomethyl resonance signals.

§ Irradiation at 253.7 nm of diastereomerically pure (**6a**) in *n*-heptane for 0.5 h gave a 55:45 mixture of (**6a**) and (**6b**), but (**4**) was not photoepimerized under these conditions.

Overall retention for the sequences (1) → (5) → (7) and (4) → (6) → (7) allows for two alternatives: either the thiomethylation and Grignard displacement steps both proceed with retention, or both steps proceed with inversion. Thus, contrary to reported precedent,^{6,7} either the Grignard displacements [(5) → (7) and (6) → (7)] take place with retention, or the thiomethylations [(1) → (5) and (4) → (6)]

with inversion. Studies to decide between these alternatives are in progress.

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